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N-cadherin expression level as a critical indicator of invasion in non-epithelial tumors

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Cancer cell dissemination away from the primary tumor and their ability to form metastases remain the major causes of death from cancer. Understanding the molecular mechanisms triggering this event could lead to the design of new cancer treatments. The establishment and the maintenance of tissue architecture depend on the coordination of cell behavior within this tissue. Cell-cell interactions must form adhesive structures between neighboring cells while remaining highly dynamic to allow and control tissue renewal or remodeling. Among intercellular junctions, cadherin-based adherens junctions mediate strong physical interactions and transmit information from the cell microenvironment to the cytoplasm. Disruption of these cell-cell contacts perturbs the polarity of epithelial tissues leading to their disorganization and ultimately to aggressive carcinomas. In non-epithelial tissues, the role of cadherins in the development of cancer is still debated. We recently found that downregulation of N-cadherin in malignant glioma—the most frequent primary brain tumor—results in cell polarization defects leading to abnormal motile behavior with increased cell speed and decreased persistence in directionality. Re-expression of N-cadherin in glioma cells restores cell polarity and limits glioma cell migration, providing a potential therapeutic tool for diffuse glioma.

Keywords: cadherin, adherens junctions, migration, invasion, polarity, astrocyte, glioma, glioblastoma

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Introduction

The migration of cancer cells blurs tumor margins and possibly leads to metastases. Tumor invasion frequently prevents the success of focal therapies such as surgery or radiotherapy and constitutes a major obstacle on the road to cancer treatment. It is thus essential to better understand the mechanisms responsible for cancer cell invasion. The process of cell migration has been widely studied over the last decades and the main molecular components required for cell motility have been deciphered.[1-3] Numerous regulators of the cytoskeleton have been found to be overactivated in cancers. According to various studies led in breast, colon and lung cancers (for a review, see ref. 4), Rho GTPases proteins (Rac1, Cdc42, RhoA and RhoC) show a higher activity in cancer cells than in normal cells. The PI3K pathway, involved in the very first steps of cell migration, is also overactivated in a wide range of tumors such as prostate, breast, endometrium, colon and nervous system cancers, due to *Pik3ca* activating mutations[5] and/or *Pten* deletion (for a review see ref. 6) and is linked to invasive forms of these tumors.[7]

If the overactivation of the motility machinery is a well-known feature of invasive cells, the relationship between cancer cells and their microenvironment is another fundamental topic which, in contrast, has not been fully explored. To coordinate the intracellular forces generated by the cell cytoskeleton and produce a net displacement, cells must acquire a structural asymmetry that discriminates the cell front from the cell rear. The polarization and the orientation of the cell are tightly controlled by extracellular cues and cancer cell dissemination certainly requires profound alterations of these regulatory mechanisms. In vitro

and in vivo experiments have shown that decreased adhesion to the substratum or to the surrounding epithelial cells favors the invasion process of carcinoma cells leading ultimately to metastasis[8-10] (for a review see ref. 11). These changes can result from oncogenic pathways, such as increased TGF-β or Wnt signaling,[12,13] which ultimately destabilize the epithelial barrier, or from abnormal levels of adhesion molecules at the plasma membrane. We have recently demonstrated that alterations in the expression level of the intercellular adhesion molecule N-cadherin in glia-derived tumors lead to dramatic changes in the migratory behavior of cancer cells.

Pertubation of Cadherin Levels in Gliomas

The integrin family of cell adhesion receptors directly binds components of the extracellular matrix providing the traction force necessary for cell motility and invasion. The expression level of integrins is frequently altered in cancers. Such alterations are associated with increased or decreased cell invasion depending on the adhesive properties of the integrin but also on the cell context and the tumor stage.[11,14] Similarly, altered expression of the intercellular adhesion molecules coincides with tumor progression and increased dissemination.[15]

Among the various molecular complexes involved in cell-cell interactions, adherens junctions allow calcium dependent cell-cell adhesion and play a key role in maintaining tissue integrity. Classical cadherins are essential transmembrane components of adherens junctions. E-cadherin is mainly expressed in epithelial tissues[16] and loss of E-cadherin is viewed as a triggering event of carcinoma cell detachment from the primary tumor and invasion of the conjunctive tissues.[9,17] The decrease of E-cadherin expression is frequently associated with a cadherin switch resulting in the concomitant increase in N-cadherin expression.[18-20] In contrast to E-cadherin, the expression of N-cadherin molecules in these cells seems to have a promigratory effect, promoting tumor infiltration in the conjunctive tissue,[21,22] possibly by favoring association of cancer cells with endothelial and other stromal cells. Although the changes in cadherin levels during carcinoma progression are now well documented, the possibility that such changes occur in non-epithelial tumors has only recently begun to be explored.

Gliomas account for more than 50% of all brain tumors and are the most common primary brain tumors in adult. Its malignant forms are associated with one of the poorest prognoses for cancer because of their ability to infiltrate diffusely into the normal cerebral parenchyma. The causes of glioma invasion remain poorly understood. Various studies have shown that changes in N-cadherin levels occur in malignant gliomas.[23-26] Some results show an inverse correlation between N-cadherin expression and glioma invasiveness.[23,27] Others do not show any correlation[26] and even report a positive correlation with the grade of the gliomas, knowing that the higher the grade is, the more invasive gliomas are.[24] This apparent contradiction may result from the use of different animal models or from the fact that, in some studies, the level of N-cadherin mRNA is analyzed, while other studies are based on the level of N-cadherin protein. In our recent study,[28] we have used fresh malignant glioma samples, tumor-derived primary glioma cells and commercial glioma cell lines. We observed that the level of N-cadherin protein is variable but is generally lower in tumor samples and in tumor cells than in normal brain and primary glial cells. Surprisingly, we observed that mRNA levels were, in contrast, higher in tumor samples than in normal tissues (Péglion, unpublished data). These seemingly contradictory results may reflect a decrease in protein stability that would need to be confirmed. They may also explain the discrepancy between previous reports. A downregulation of the catenins, major protein partners of cadherin, was also observed in glioma cells, strengthening the idea of a decrease in N-cadherin protein levels and further showing that adherens junctions are destabilized in glioma cells. Decreased cell-cell adhesion was also confirmed after staining of adherens junction components in glioma cells. Alteration of cell-cell adhesion was associated with an abnormal migratory behavior in vitro, suggesting that changes in cadherin expression levels may play a key role in tumor invasion.

N-Cadherin in Control of Cell Migration

Cadherins are adhesive molecules that transmit most of the mechanical forces exerted between neighboring cells. As such, they strongly contribute to tissue integrity. In addition, N-cadherin has been shown to serve as a support for neurons that migrate in a chain-like fashion.[29] In some circumstances, they may also function as a brake for cell migration.[30] In glioma cells, downregulation of adherens junction molecules was associated with an increased velocity when cell migration was tested in a wound-healing in vitro assay. In this assay, normal glial cells migrate slowly as a cohesive sheet. Downregulation of N-cadherin levels led to the detachment of wound-edge cells from the monolayer, suggesting that alteration of adherens junctions may release a brake caused by cell-cell adhesion at the cell rear. However, the migration induced by wounding a 2D confluent cell monolayer is very different from the migration observed during tumor cell invasion. We thus also analyzed the cell migratory behavior in a 3D matrigel spheroid assay, closer to physiological conditions. Decreasing the expression of N-cadherin by siRNA increased glial cell invasion in the surrounding matrigel, mimicking the dispersion of glioma cells in this assay (Péglion, unpublished data). It is thus tempting to speculate that, in neural as in epithelial tissues, loss of the adhesion molecules responsible for tissue cohesion favors the escape of tumor cells from the tissue of origin.

Once free from the original tumor, N-cadherin expressing carcinoma and glioma cells migrate between cells also expressing N-cadherin. There, the versatility of N-cadherin in the control of migration speed may result from different expression levels of this molecule at the cell surface and in the cell microenvironment. Variations in the role of N-cadherin in cell migration may also result from differences in the expression of protein partners such as catenins, between cell types.[31-33] Cadherin regulators, such as the ubiquitine ligase Hakai, may be expressed in

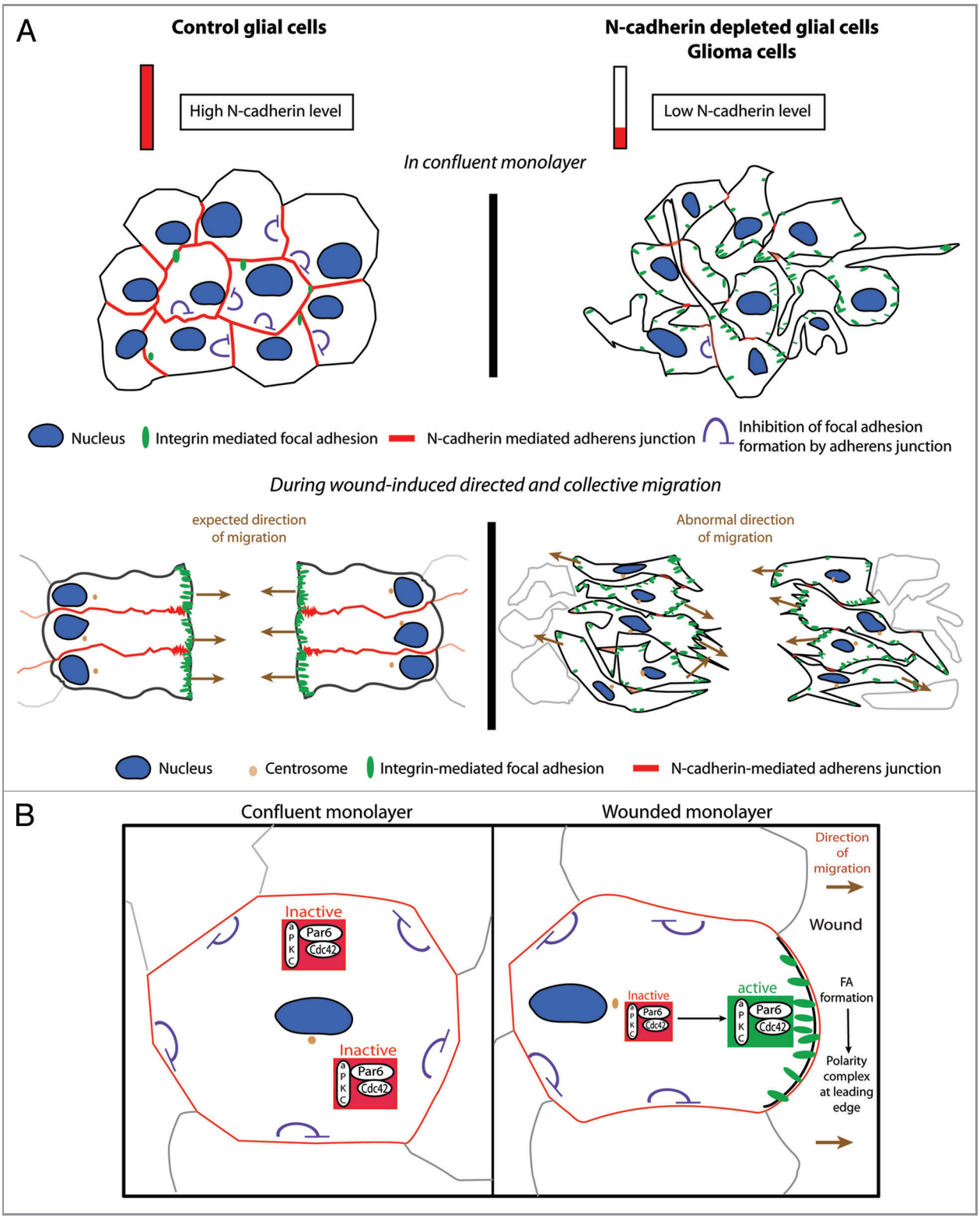

Figure 1. N-cadherin expression level affects astrocyte adhesion, polarity and migration. (A) N-cadherin-mediated cell-cell contacts locally inhibit the formation of focal adhesions (FAs). As a consequence, glioma cells, which express less N-cadherin (right side), have less adherens junctions and more FA around their periphery than normal astrocytes (left side). During wound healing, normal astrocytes at the wound edge display anisotropic cell-cell contacts. FAs form and accumulate at the cell wound edge, promoting cell polarization and directed migration. In contrast, in cells lacking N-cadherin, the distribution of FAs is not polarized and the direction of migration is random. (B) In confluent astrocytes, removal of cell-cell contacts by wounding of the monolayer allows the formation of FA at the wound edge. This induces an intracellular signal promoting the recruitment and activation of the polarity complex Cdc42-Par6-aPKC.

transformed epithelial cells but not in neural cells.[34,35] How such variation may affect the functions of N-cadherin remains to be elucidated. The expression levels of these proteins and also the expression of cell-type specific isoforms may affect cadherin stability at the plasma membrane, adherens junctions' turnover or cadherin-mediated intracellular signals.

In addition to faster migration, we also observed that a decrease in N-cadherin levels induced a less persistent movement, with cells frequently turning and changing direction. This phenomenon was associated with a perturbation of the front-rear polarity axis in these cells and suggested that N-cadherin may also play a key role in the regulation of cell polarity. Beyond its mechanical role, N-cadherin can also transduce intracellular signals which could indirectly affect cell migration.[36] Cadherin-mediated signals have been involved in the regulation of cell polarity and may thereby affect the direction of migration. In epithelial cells, there is a strong interdependent relationship between adherens junction formation and baso-apical polarity determination (for a review, see ref. 37). Baso-apical polarity in epithelial cells is defined by the appropriate segregation of three different polarity complexes, which are the Par, the Crumbs and the Scribble complexes.[38-40] Cadherins have been linked to polarity complexes either via their direct interaction with members of the polarity complexes or via the regulation of the small GTPases and specific phospholipids which controls the asymmetric distribution of polarity complexes in epithelial cells. Par3, a member of the Par complex, has indeed been shown to localize at cadherin-dependent cell-cell junctions[41] and to interact with VE-and N-cadherin complexes. Loss of E-cadherin perturbs the localization of aPKC, another member of the Par complex. E-cadherin can also interact with Dlg a member of the Scribble complex[42] (for a review see ref. 37). In addition, E-cadherin contributes to the polarized targeting of basolateral membrane components via its interaction with the exocyst complex.[43]

Essential to baso-apical polarity, cadherins are also involved in the front-rear polarization of wound edge cells.[44,45] Anisotropic distribution of cadherin-mediated interactions sets the direction of the centrosome-nucleus polarity axis in astrocytes. As a consequence, cells that cannot maintain N-cadherin-mediated junctions are unable to polarize properly. We propose that this causes frequent changes in the orientation of the polarity axis and, in consequence, in the direction of migration. A similar behavior is observed in glioma cells that express low levels of cadherins. In these cells the centrosome is mispositioned and the direction of migration induced by wounding continuously varies (**Fig. 1A**, lower panel). Importantly, re-expression of N-cadherin in glioma cells restores centrosome orientation and normal cell polarity, indicating that the decrease in N-cadherin levels is a major event leading to perturbation of cell polarity in glioma cells.

How cadherins actually control front-rear polarity during collective migration is still not fully understood. In fact, integrins signaling has been previously shown to be required for polarization of migrating astrocytes.[46,47] Formation of new focal adhesions is restricted to the leading edge. Integrin signaling leads to the polarized recruitment and activation of the polarity complex Par6-aPKC via the small G protein, Cdc42 (**Fig. 1B**). In gliomas or in N-cadherin depleted astrocytes, the distribution of focal adhesions is not polarized. In normal cells, the presence of adherens junctions locally inhibits the formation of focal adhesions.[44,48] Thus, in a confluent monolayer, very few focal adhesions are present. During neural crest cell migration, N-cadherin-mediated junctions also inhibit Rac activation and therefore restrict its activity to the free edge,[49] where it can induce the formation of new focal contacts. In absence of stable adherens junctions, focal adhesions are present all around the cell periphery (**Fig. 1A**, upper panel), and the release of cell-cell contacts by wounding does not induce new integrin-mediated interactions. In these conditions, the recruitment of Cdc42 does not occur and cell orientation remains random.

Conclusion

Our current understanding of the events leading to non-epithelial tumor spreading, such as gliomas, mainly relies on anatomical studies and, more recently, on rodent models and orthotopic xenograft of glioblastoma cells.[50] A better comprehension of the mechanisms responsible for tumor cell migration is essential to find new therapeutic targets and to avoid relapses after classic treatments. Glioma cells can invade and spread into the brain parenchyma over long distances. It is not a metastatic process but an active dissemination either along pre-existing structures such as myelinized axons or perivascular spaces, or through the cerebrospinal fluid.[51] The therapeutic challenge for glioma invasion is however the same as for metastatic cancers: it aims at preventing the detachment of cancerous cells from the initial tumor mass to limit their dissemination. Re-introducing N-cadherin in glioma cells in vitro rescues glioma cell polarity and limits their migration. These findings need to be validated in vivo, but lead us to think that restoring cadherin cell-cell contacts in glioma cells may reduce glioma invasion and could become a new potential therapeutic strategy for glioma treatment.

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